REMARKS

Amendments to the Claims

Claims 1-17, 31-43, 48-61, 63, 67-73 93, 94, 99-101, 114-121 and 123-135 are pending. The Applicant thanks the Examiner for withdrawing the restriction requirement against Claims 48-53. The Applicant respectfully asks the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1-16, 31, 33-43, 54, 55, 58-61, 114, 115, 118-121, 123, 124, 127 and 131 were amended; Claims 93, 94, 96, 97, 99-101, 134 and 135 were canceled; and Claim 136 is new. The Applicant states that all amended claims do not add new subject matter to the present specification.

Support for the phrase "two or more" in Claim 1 can be found throughout the specification, such as, *e.g.*, ¶¶ 57, 78, 79, 87, and original Claim 1.

Support for the phrase "directing" in Claims 1, 12 and 54 can be found throughout the specification, such as, *e.g.*, ¶¶ 57, 68, 83 and 210.

Claim Objections

The Examiner has objected to Claims 1-11, 14-17, 33-35, 124, 131 and 134 for lacking a comma before the recitation of the "wherein" clauses. The Applicant has amended all claims to include a comma in the appropriate places. Thus, the Applicant respectfully requests withdrawal of the objection against Claims 1-11, 14-17, 33-35, 124, 131 and 134.

The Examiner has objected to Claims 1-11 and 14-17 for reciting an improper Markush group format. The Applicant has amended all claims to recite a proper Markush group format. Thus, the Applicant respectfully requests withdrawal of the objection against Claims 1-11 and 14-17.

The Examiner has objected to Claims 12-13 and 15-17 for reciting a combination of claim limitations twice. The Applicant has amended all claims by deleting the second recitation.

Thus, the Applicant respectfully requests withdrawal of the objection against Claims 12-13 and 15-17.

The Examiner has objected to Claims 127 and 135 for having a period at the end of paragraph 1 and before the "wherein" clause. The Applicant has amended all claims to delete the period. Thus, the Applicant respectfully requests withdrawal of the objection against Claims 127 and 135.

Rejection Pursuant to 35 U.S.C. § 101

The Examiner has rejected Claims 134 and 135 as allegedly lacking utility under 35 U.S.C. §101 because the claimed subject matter is directed toward non-statutory subject matter. The Applicant has cancelled Claims 134 and 135 for reasons unrelated to this rejection. However, such cancellation has rendered this rejection immaterial. Thus, the Applicant respectfully requests withdrawal of the 35 U.S.C. §101 utility rejection against Claims 134 and 135.

Rejection Pursuant to 35 U.S.C. 112, ¶ 2

I. Open and closed language

The Examiner has rejected Claims 1-17 as allegedly being indefinite under 35 U.S.C. § 112, ¶ 2 for reciting language that is unclear. Thus, the Applicant respectfully submits that amended Claims 1-17 are definite and request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefiniteness rejection against Claims 1-17.

II. "Stimulate" and "produce"

The Examiner has rejected Claims 31-43 as allegedly being indefinite under 35 U.S.C. § 112, ¶ 2 for reciting "producing" instead of "stimulating" because a peptide fragment can stimulate but not produce an immune response. Claims 31-43 have been amended to recite "stimulating" instead of "producing." Thus, the Applicant respectfully submits that Claims are

definite and request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefiniteness rejection against Claims 31-43.

III. Insufficient antecedent basis

The Examiner has rejected Claims 36-43 as allegedly being indefinite under 35 U.S.C. § 112, ¶ 2 for lacking antecedent basis for recited claim limitations The Applicant respectfully submits that amended Claims 36-43 are definite and request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefiniteness rejection against Claims 36-43.

IV. Determining step

The Examiner has rejected Claims 1-17, 54-61, 63, 67-73 as allegedly being indefinite under 35 U.S.C. § 112, ¶ 2. The Examiner asserts that the recitation of "determining" in the Claims sets forth the mental step and not a positive methods step that utilizes reagents. The Applicant respectfully disagrees with the Examiners assertion that "determining" is a mental step and not a positive methods step that utilizes reagents. However, only for the sake of expediting prosecution, the Applicant has amended Claims 1-17, 54-61, 63, 67-73 to recite "detecting" instead of "determining." Thus, the Applicant respectfully submits that the amended Claims are definite and request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefiniteness rejection against Claims 1-17, 54-61, 63, 67-73.

I. Non-immunogenic peptides

The Examiner has rejected Claims 31-42, 114-121, and 123-133 allegedly being indefinite under 35 U.S.C. § 112, ¶ 2. The Examiner asserts that the claims do not clearly set forth the invention of administering an immunoreactive fragment in order to produce or induce an immune response. This is because, the Examiner contends, that the recited phrase "an immunoreactive BoNT/A amino acid sequence fragment thereof" encompasses sequence fragments that could be as small as two amino acids in length, and as such, covers peptide fragments unable to be recognized by the host's animal immune system. The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

Step (a) of Claim 31 recites, in part, "wherein said immunoreactive BoNT/A amino acid sequence fragment stimulating an immune response comprises at least six consecutive amino acids of 785-803 of SEQ ID NO: 1." Step (c) of Claim 31 recites, in part, "wherein said immunoreactive BoNT/A amino acid sequence fragment stimulating an immune response comprises at least six consecutive amino acids of 981-999 of SEQ ID NO: 1, at least six consecutive amino acids of 1051-1069 of SEQ ID NO: 1, at least six consecutive amino acids of 1121-1139 of SEQ ID NO: 1 or at least six consecutive amino acids of 1275-1296 of SEQ ID NO: 1." As such no immunoreactive BoNT/A amino acid sequence fragment thereof" can be as small as two amino acids in length because all must be "at least six consecutive amino acids" in length. As Claims 32-43 are dependent on Claim 31, all these Claims incorporate by reference this "at least six consecutive amino acid" length limitation.

Similarly, Claim 114 recites, in part, "wherein said immunoreactive BoNT/A amino acid sequence fragment of amino acids 785-794 of SEQ ID NO:1 stimulating an immune response comprises at least six consecutive amino acids of 785-794 of SEQ ID NO: 1." Likewise, Claim 115 recites in part, "wherein said immunoreactive BoNT/A amino acid sequence fragment stimulating an immune response comprises at least six consecutive amino acids of 785-803 of SEQ ID NO: 1, at least six consecutive amino acids of 981-999 of SEQ ID NO: 1, at least six consecutive amino acids of 1051-1069 of SEQ ID NO: 1, at least six consecutive amino acids of 1121-1139 of SEQ ID NO: 1 or at least six consecutive amino acids of 1275-1296 of SEQ ID NO: 1." As such no immunoreactive BoNT/A amino acid sequence fragment thereof" can be as small as two amino acids in length because all must be "at least six consecutive amino acids" in length. As Claims 116-121 are dependent on either Claim 114 or 115, all these Claims incorporate by reference this "at least six consecutive amino acid" length limitation.

Claim 123 recites, in part, "wherein said immunogenic BoNT/A amino acid sequence stimulating an immunogenic response comprises at least six consecutive amino acids of 491-509 of SEQ ID NO: 1, at least six consecutive amino acids of 519-537 of SEQ ID NO: 1, at least six consecutive amino acids of 533-551 of SEQ ID NO: 1, at least six consecutive amino acids of 547-565 of SEQ ID NO: 1, at least six consecutive amino acids of 589-607 of SEQ ID NO: 1, at least six consecutive amino acids of 631-649 of SEQ ID NO: 1, at least six

consecutive amino acids of 659-677 of SEQ ID NO: 1, at least six consecutive amino acids of 673-691 of SEQ ID NO: 1, at least six consecutive amino acids of 715-733 of SEQ ID NO: 1, at least six consecutive amino acids of 743-761 of SEQ ID NO: 1, at least six consecutive amino acids of 771-789 of SEQ ID NO: 1, at least six consecutive amino acids of 785-803 of SEQ ID NO: 1, at least six consecutive amino acids of 813-831 of SEQ ID NO: 1 or at least six consecutive amino acids of 827-845 of SEQ ID NO: 1." As such no immunoreactive BoNT/A amino acid sequence fragment thereof" can be as small as two amino acids in length because all must be "at least six consecutive amino acids" in length. As Claims 124-133 are dependent on Claim 123, all these Claims incorporate by reference this "at least six consecutive amino acid" length limitation.

Thus, the Applicant respectfully submits that the immunoreactive BoNT/A amino acid sequence fragments must either be at least six amino acids in length. These sequence lengths are sufficient to stimulate an immune response. Therefore, the Applicant respectfully submits that the Claims are definite and request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefiniteness rejection against Claims 31-42, 114-121, and 123133.

Rejection Pursuant to 35 U.S.C. § 102(b)

I. Tugnoli Reference in light of Domlimbek Reference

The Examiner has rejected Claims 1-15, and 17 as allegedly anticipated under 35 U.S.C. §102(b) by Valeria Tugnoli et al., *The Therapeutic Use of Botulinum Toxin*, 6(10) Exp. Opin. Invest. Drugs 1383-1394 (1997), hereafter the "Tugnoli reference" in light of evidence provided by Behzod Z. Dolimbek et al., *Mapping of the Regions on the Heavy Chain of Botulinum Neurotoxin A (BoNT/A) Recognized by Antibodies of Cervical Dystonia Patients with Immunoresistance to BoNT/A*, 44(5) Mol. Immunol. 1029-1041 (2007), hereafter the "Domlimbek reference." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

According to *MPEP* § 2131, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d

1051, 1053 (Fed. Cir. 1987). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1576 (Fed. Cir. 1991).

According to § *MPEP* 2131.01, "a 35 U.S.C. § 102 rejection over multiple references has been held to be proper when the extra references are cited to: . . . (C) show that a characteristic not disclosed in the reference is inherent. Although "[i]t is sometimes appropriate to consider extrinsic evidence to explain the disclosure of a reference. Such factual elaboration is necessarily of limited scope and probative value, for a finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations." Scripps Clinic, 927 F.2d at 1676. Furthermore, the use of a secondary reference can only be used to explain, but not expand, the meaning of the anticipatory reference. "The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference. Id. Thus, while a secondary reference may be used to indicate what an anticipatory reference would have meant to a person of ordinary skill in the art, "it is error to build "anticipation" on a combination of these references." Id. "If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not § 102 anticipation, but § 103 obviousness." Id. at 1576-77. Thus, although additional references may be used to confirm the contents of the allegedly anticipating reference, anticipation does not permit an additional reference to supply a missing claim limitation.

Currently amended Claims 1-15, and 17 are directed towards BoNT/A peptides limited to a length of 19 amino acids.

The Examiner has stated that the Tugnoli reference does "not disclose the specific peptides the antibodies in the individual immunoreact." November 22, 2006 Office Action at pg. 6, point 10, lines 4-5. In fact, this reference does not expressly or inherently disclose the identity of any of the reagents use in either the mouse bioassay or the ELISA mentioned. Thus, this reference does not expressly or inherently disclose the specific BoNT/A peptides

presently claimed. Furthermore, since the presently claimed BoNT/A peptide are not disclosed in the Tugnoli reference. there is nothing for the Domlimbek reference to explain. The Domlimbek reference was inappropriately used to fill in the gaps of the elements missing from the Tugnoli reference.

Thus, the disclosure of the mouse bioassay or ELISA in the Tugnoli reference is not anticipatory because this reference does not expressly or inherently disclose the specific BoNT/A peptides presently claimed. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1-15, and 17.

II. Jankovic Reference in light of Domlimbek Reference

The Examiner has rejected Claims 1-13, and 17 as allegedly anticipated under 35 U.S.C. §102(b) by Joseph Jankovic and Kenneth Schwartz, *Response and Immunoresistance to Botulinum Toxin Injections*, 45(9) Neurology 1743-1746 (1995), hereafter the "Jankovic reference" in light of evidence provided by Behzod Z. Dolimbek et al., *Mapping of the Regions on the Heavy Chain of Botulinum Neurotoxin A (BoNT/A) Recognized by Antibodies of Cervical Dystonia Patients with Immunoresistance to BoNT/A*, 44(5) Mol. Immunol. 1029-1041 (2007), hereafter the "Domlimbek reference." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

First, the Examiner has stated that the Jankovic reference does "not disclose the specific peptides the antibodies in the individual immunoreact." November 22, 2006 Office Action at pg. 7, point 12, lines 5-6. Thus, this reference does not expressly or inherently disclose the BoNT/A peptides presently claimed and is not an anticipatory reference. Furthermore, since the presently claimed BoNT/A peptide are not disclosed in the Jankovic reference. there is nothing for the Domlimbek reference to explain. The Domlimbek reference is inappropriately used to fill in the gaps of the elements missing from the Jankovic reference.

Second, the Jankovic reference discloses the use of a mouse bioassay. Jankovic, 45(9) Neurology at pg. 1744, col. 1, ¶ 2, lines 1-2. A BoNT/A mouse bioassay is an in vivo toxin neutralization test that does not use BoNT/A peptides. In this assay, a patient's serum sample is mixed together with BoNT/A, and, after an incubation period, is injected into mice.

The presence of neutralizing anti-BoNT/A antibodies is measured by the survival rate of the mice. If the patient's blood contains neutralizing anti-BoNT/A antibodies, then these antibodies bind to the neurotoxin inactivate it. Because the neurotoxin is inactivated, injected mice survive, thereby indicating the presence of neutralizing anti-BoNT/A antibodies. On the other hand, if a patient's serum lacks neutralizing anti-BoNT/A antibodies, the neurotoxin remains active. As such, injected mice die, thereby indicating the absence of neutralizing anti-BoNT/A antibodies. As such, the Jankovic reference does not teach the specific BoNT/A peptides presently claimed in the mouse bioassay disclosed.

Thus, the disclosure of a mouse bioassay in the Jankovic reference is not anticipatory because this reference does not expressly or inherently disclose the specific BoNT/A peptides presently claimed. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1-13, and 17.

III. Hanna Reference in light of Domlimbek Reference

The Examiner has rejected Claims 1-13, and 17 as allegedly anticipated under 35 U.S.C. §102(b) by Philip Hanna and Joseph Jankovic, *Mouse Bioassy Verses Western Blot Assay for Botulinum Toxin Antibodies: Correlation with Clinical Response*, 50(6) Neurology 1624-1629 (1998), hereafter the "Hanna reference" in light of evidence provided by Behzod Z. Dolimbek et al., *Mapping of the Regions on the Heavy Chain of Botulinum Neurotoxin A (BoNT/A) Recognized by Antibodies of Cervical Dystonia Patients with Immunoresistance to BoNT/A*, 44(5) Mol. Immunol. 1029-1041 (2007), hereafter the "Domlimbek reference." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

First, the Examiner has stated that the Hanna reference does "not disclose the specific peptides the antibodies in the individual immunoreact." November 22, 2006 Office Action at pg. 7, point 14, lines 3-4. Thus, this reference does not expressly or inherently disclose the BoNT/A peptides presently claimed and is not an anticipatory reference. Furthermore, since the presently claimed BoNT/A peptide are not disclosed in the Hanna reference. there is nothing for the Domlimbek reference to explain. The Domlimbek reference is inappropriately used to fill in the gaps of the elements missing from the Hanna reference.

Second, the Hanna reference discloses the use of a mouse bioassay and a Western blot assay (WBA). As discussed above, disclosure of a mouse bioassay does not read on the presently claimed method because this assay does not use BoNT/A peptides of any sort, let alone the BoNT/A peptides presently claimed. The disclosure of the WBA is also not anticipatory. The Hanna reference indicates that the WBA uses "a BoNT/A antigen." Hanna, 44(5) Mol. Immunol. at pg. 1625, col. 1, ¶ 3, line 12. However, which BoNT/A antigen is not indicated. For instance, it is not disclosed whether the BoNT/A antigen is the full length neurotoxin, the heavy chain fragment, the light chain fragment, or any one of a vast array of BoNT/A peptide fragments that could immunoreact with an anti-BoNT/A antibody. As such, the Hanna reference does not teach the specific BoNT/A peptides presently claimed in the mouse bioassay or WBA disclosed.

Thus, the Hanna reference is not an anticipatory because this reference does not expressly or inherently disclose the specific BoNT/A peptides presently claimed. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1-13, and 17.

IV. Oshima Reference

The Examiner has rejected Claims 1-11, 14, 16 and 17 as allegedly anticipated under 35 U.S.C. §102(b) by Minako Oshima et al., *Immune Recognition of Botulinum Neurotoxin Type A: Regions Recognized By T Cells and Antibodies Against The Protective H_C Fragment (Residues 855-1296) of the Toxin*, 34(14) Mol. Immunol. 1031-1040 (1997), hereafter the "Oshima reference." The Applicant respectfully asks for reconsideration pursuant to 37 C.F.R. § 1.111.

The presently claimed method recited by Claim 1 has always been directed to the use of two or more BoNT/A peptides selected from two different groups. Group one includes a BoNT/A peptide consisting of an amino acid sequence selected from the group consisting of amino acids 785-803 of SEQ ID NO: 1, a conservative BoNT/A amino acid sequence variant thereof and an immunoreactive BoNT/A amino acid sequence fragment thereof. Group two includes a BoNT/A peptide consisting of an amino acid sequence selected from the group consisting of amino acids 981-999 of SEQ ID NO: 1, amino acids 1051-1069 of SEQ ID NO:

1, amino acids 1121-1139 of SEQ ID NO: 1, amino acids 1275-1296 of SEQ ID NO: 1, a conservative BoNT/A amino acid sequence variant thereof and an immunoreactive BoNT/A amino acid sequence fragment thereof. The Applicant has amended Claim 1 to more clearly indicate the claimed method.

The Oshima reference does not disclose a Group one BoNT/A peptide. Thus, the Oshima reference is not an anticipatory because this reference does not expressly or inherently disclose the specific BoNT/A peptides presently claimed. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1-11, 14, 16 and 17.

V. Anticipation rejections against Claims 93, 94, 96, 97 and 134.

Claims 93, 94, 96, 97 and 134 were canceled for reasons unrelated to the alleged anticipation rejections raised by the Examiner. However, such cancellation has rendered the anticipation rejections immaterial. Therefore, the Applicant respectfully requests withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93, 94, 96, 97 and 134.

CONCLUSION

For the above reasons the Applicant respectfully submits that the claims are in condition for allowance, and the Applicant respectfully urges the Examiner to issue a Notice to that effect. Should there be any questions, the Examiner is invited to call the undersigned agent. Please use Deposit Account 01-0885 for the payment of any extension of time fees pursuant to 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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